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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/848,967	05/04/2001	Emanuel Calenoff	21417/92378	6936

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/848,967	CALENOFF ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,17-19,21 and 22* is/are pending in the application.

4a) Of the above claim(s) *4-16 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,17-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *6/14/2006* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment tiled on 3/27/2006has been received and entered into record and considered.

Claims 1-3, 17-19 and 21-22 are under examination. Claims 4-16 and 20 are withdrawn from further consideration.

1. The rejections of claims 1-3, 17-19, 21 & 22 under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth in the 12/30/2005 Office Action are maintained.

2. The rejections of claims 1-3, 17-19, 21 & 22 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, as set forth in the 12/30/2005 Office Action are maintained.

Comparative Protein

3. Claims 1-3, 17-19, 21 & 22 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Step (d) of amended claim 1 requires that the peptides of the claim have "an amino acid net sequence homology of 50 percent or less as compared with contiguous amino acid sequences of a comparative protein defined by a matching algorithm."

Fundamental to an understanding of the claim is what is meant by "comparative protein." The specification contains at least two definitions of "comparative proteins." In paragraph [008] occurs a definition:

> (c) a net amino acid sequence homology of less than 50 percent as compared to the structure of peptide regions on proteins of related non-target proteins (the "comparative" proteins);

whereas paragraph [067] states

> Computer-aided searches are performed to locate at least two amino acid sequences that show no more than 50% homology with the target protein. These sequences are designated non-targeted, non-specific or comparative proteins.

It is noted that the definition in paragraph [067] is followed by an example of two related polypeptides.

In the response of February 18, 2004 applicant stated

> However, "**comparative proteins**" are extensively defined in the specification e.g., on page 2 , lines 35-36 to page 3, lines 1-7, and page 12, lines 29-31, the specification describes "comparative proteins" as non-targeted and non-specific proteins that show no more than 50% homology with the targeted protein as determined by computer-aided analysis.

The examiner does not find the cited passages provide an extensive definition whatsoever especially when read in conjunction with applicant's remarks.

The definitions at [008] and [067] are not the same. The definition of [008] requires that the sequence of a peptide share less than 50% homology to the sequence in the polypeptide to which it is aligned whereas [067] requires that the sequence of the polypeptides from which the peptide sequence arises share less than 50% homology.

The response of July 16, 2004 was accompanied by an Expert Declaration and addressed in part the issue of "comparative proteins." Dr. Anderson states in paragraph 4. b.

> . . .Then follows the unique and inventive steps of Calenoff-Ditlow: The protein surface probable sequences (the PSP sequences) are compared to all other known proteins (comparative proteins) for possible sequence homologies and those which are less than 50% homologous to sequences of other proteins, and which have less than 4 or more contiguous amino acids identical to the comparative protein sequences, are selected for use as immunogens and are the peptides for which composition claims are made.

In the response of April 25, 2005 applicant states

A peptide satisfying 1 (a) (b) and (c) is then tested against other peptides of the same length, that is, from "comparative proteins", **not** from the target protein. This is to eliminate peptides that cross react with the non-target proteins.

The response also includes a table designated **Comparative Proteins** at page 10 which more extensively defines comparative proteins. Note particularly the citation to page 3, lines 23-26 of the specification which state:

[0010] Non-target proteins are selected for comparative purposes, by scanning for all available sequence matches in computer data banks. Amino acid sequences of at least 4 in length are selected from at least 1 of the protein sequences that showed some degree of homology to the target protein. Closest matches are preferred.

and to page 5, lines 5-34

[0012] To reiterate, for the methods of the present invention, a disease or condition is targeted, for which an organism, agent or tissue is identified that is known to be causative of, or associated with, the targeted disease or condition for which diagnosis and/or treatment is sought. Proteins from the organism, agent or tissue are selected from databases, e.g. the NIH gene bank, which is available on the internet. These proteins are called "target" proteins. Functionally specific peptide antigen candidates are identified from within the amino acid structure of each protein on the basis of being hydrophilic and therefore likely to be on the outer surface of the protein. The amino acid structure of the candidate peptides are then compared to the amino acid structures found in individual non-target, (non-specific), proteins by using computer matching programs such as BLAST. Functionally specific peptide antigens are selected on the basis of having no more than 50% amino acid matching (sequence homology) with the comparative protein peptide sequences. Furthermore, whatever candidate antigen sequences satisfy this criteria must also possess no more than three contiguous (immediately adjacent to one another) amino acids which are sequentially homologous to amino acids matching foreign protein amino acid sequences.

and to page 6, lines 7-10

[0016] (c) a net sequence homology of 50 percent or less as compared to the structure of single non-specific proteins, that is proteins from non-target microorganisms, or proteins from non-target tissues.

In the final three portions of the Table applicant provides an example purportedly in keeping with the definition of comparative protein as set forth earlier in the table. These portions relate to the comparison of H. pylori sequences to two related sequences.

All of the foregoing creates a paradox as to what a "comparative protein" is and how one goes about choosing comparative proteins so as to practice the invention.

If one accepts the definition set forth by applicant's declarant then candidate peptides which meet steps 1(a)-(c) would be screened using a program such as BLAST and only those which showed less than 50% homology to contiguous sequences in the data base would be selected for further testing as set forth in steps (e) and (f).

In disputing a prior art rejection applicant (Response of October 7, 2005) stated that the peptides of Malorny did not satisfy the claims because the peptide sequences were found in a plurality of polypeptides (see pages 8-9 of the response). This line of argument is consistent with the interpretation set forth by applicant's declarant.

However, applicant's specification clearly and convincingly contradicts the foregoing.

SEQ ID NO: 21 is clearly indicated as an embodiment of the instantly claimed invention, see page 12 of the specification brief description of Figure 8. Therefore, these sequences must necessarily meet the requirements of steps (d)-(f). Attached is a partial comparison run on NCBI BLAST which clearly shows that neither cited sequence meets the criteria of steps (d)-(f), see the results starting at page 15 of the Blast prinout.

One is now left to search the specification for a definition of "comparative proteins" which will permit one to obtain peptides which meet the criteria of steps (d)-(f) of claim 1. No such definition is present in the specification or claims as originally filed.

Consider paragraph [067] in relation to a definition of "comparative proteins." There is absolutely no explanation as to why the two sequences presented were chosen from the many available sequences in the NCBI database nor why only two were selected for purposes of comparison.

Enablement

4. Claims 1-3, 17-19, 21 & 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (*In re Wands,* 8 USPQ2d 1400-1408 (Fed.Cir. 1988), *Ex parte Forman,* 230 USPQ 546-549 (BdPtApp&Int 1986))

With respect to (1) the quantity of experimentation necessary no accurate evaluation can be made since it is not apparent if the requirements set forth in steps (d)-(f) of claim 1 can be met.

In support of this position it is noted that SEQ ID NO:21 which are asserted to be within the scope of the claims clearly fail step (d) of claim 1.

Step (e) requires that peptides within the scope of the claim share three or fewer contiguous amino acids "of the part of the comparative protein matched for over all homology." The exact meaning of this phrase is not set forth in the specification, however, if one accepts the Anderson declaration it would appear to mean that candidate peptides would not share three contiguous amino acids with any polypeptide sequence in the NCBI database.
Nor can one reasonably conclude that this step reasonably leads to the requisite epitopes given Figure 3 of Geysen et al. (1988). Figure 3 suggests that three contiguous amino acids are often critical to reactivity which permits the inference that one might select candidate antigens which do not share three contiguous so as to avoid cross reactivity, however, there is nothing which indicates that such a selection actually results in selecting candidate peptides which would not show cross reactivity.

Step (f) appears to require screening of candidate peptides against infected and control populations. The actual assays for such screening may be enabled, however, the diseases and candidate peptides which would satisfy such assays are not readily apparent because one of skill in the art cannot a priori predict which disease antigen has a reasonable probability of containing linear epitopes recognized by patient antibodies or contains T-cell epitopes.

With respect to (2) claim 1 has guidance to the extent that the steps are definite and one could attempt to follow them.

With respect to (3) there are no working examples which meet claim 1 as currently amended.

With respect to (4) the invention would appear to be directed toward obtaining unique epitopes present on antigens so that one could reliably detect the presence of said antigen with minimal expectation of false positives arising from cross reactive epitopes. Whether such a goal can be achieved is in question in view of Geysen et al. (1988) which sets forth that the probability that a polyclonal antisera will contain antibodies directed against a randomly chosen antigen as about 1 in 40.

With respect to (5) the prior art is rife with epitope predicting algorithms which have shown various degrees of efficacy.

With respect to (6) the level of skill in the art in designing algorithms and developing immunoassays is high.

With respect to (7) there are currently no algorithms in the prior art which predict unique epitopes.

With respect to (8) the claims currently embrace mixtures of peptides for any possible antigen.

Response to Applicant's arguments

Applicant's response has been thoroughly considered, however, it is not persuasive.

5. Applicant amended the claims so as to eliminate SEQ ID NO:13 from the scope of the claims. However, applicant made no amendment to the claims which would exclude SEQ ID NO:21 from the scope of the instantly claimed invention. Nor did applicant provide any argument as to how SEQ ID NO: 21 is outside the scope of the amended claims despite the examiner's having presented evidence that it is apparently outside the scope of the amended claims.

Applicant has asserted that the examiner "flounts" well established principles of patent law in questioning the enablement of the instantly claimed invention. Perhaps applicant meant "flouts." The examiner did not require clinical success, rather the examiner has provided empirical evidence that an embodiment stated in the specification as being within the scope of the instantly claimed invention fails to meet the limitations of the claims. Applicant has offered no objective rebuttal that SEQ ID NO: 21 is outside the scope of the instant claims.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jacob Cheu
Examiner
Art Unit 1641

June 15, 2006

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